REMARKS

Status of the Claims

Claims 1-8, and 10-86 are pending. Claims 40-86 are withdrawn pursuant to a Restriction Requirement and subsequent election without traverse.

Claims 1-39 stand rejected under at least one of 35 U.S.C §§ 112, 102, 103. Claim 9 is canceled. Claims 1, 13, 14, and 25 are amended. Support for the Amendment can be found throughout the Specification, including on pages 11, and 23-25.

Objection to the Specification

The disclosure was objected because it contained a hyperlink. The above amendment to the Specification removed the hyperlink on page 13. Thus, this objection is moot.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 1-39 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested. Each issue raised by the Examiner is discussed in turn, below.

Claims 1 and 13

Claims 1 and 13 are rejected because they "recite 'a 2-arachidonylglycerol (2-AG)' but it [allegedly] is not clear what the meets and bounds are for the phrase." While this position is traversed, Applicants respectfully submit that it is moot in view of the amendment. Claims 1 and 13 are amended to feature "a COX-2 specific metabolite of a 2-arachidonylglycerol compound."

Claim 14

Claim 14 was rejected due to allegedly not being clear with respect to a standard value. While this position is traversed, Applicants respectfully submit that it is moot in view of the amendment. Claim 14 is amended to clarify the standard value.

Claims 23 and 33

Claims 23 and 33 are allegedly indefinite because the recitation of "a COX-2- selective substrate" is not clear. This position is respectfully traversed.

A claim is definite within the meaning of 35 U.S.C. § 112, second paragraph, if it sets out and circumscribes a particular subject matter with a reasonable degree of clarity and particularly. See M.P.E.P. § 2173.02. Further, the Office is specifically instructed to "allow claims which define the patentable subject matter with a reasonable degree of particularly and distinctness. Id.

In the instant Application, "COX-2 selective substrate" is specifically defined in the Specification beginning on page 10. For the convenience of the Examiner, a portion of that definition is reproduced below:

> A COX-2 selective substrate is a substrate that is transformed to an enzymatic reaction product by the COX-2 enzyme; but is not transformed, or is not significantly transformed, to a reaction product by the COX-1 enzyme. ..

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the Specification. "If the claims, when read in light of the

Specification reasonable apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Miles Lab., Inc. v. Shandon, Inc.* 27 U.S.P.Q.2d 1123, 1126 (Fed. Cir. 1993).

Claims 23 and 33 clearly meet the legal standard for definiteness. One of ordinary skill in the art would understand the scope of the claims at issue to be clear. In short, if a substrate is transformed to an enzymatic reaction product by the COX-2 enzyme; but is not transformed, or is not significantly transformed, to a reaction product by the COX-1 enzyme, then the substrate is a COX-2 selective substrate of the present invention. If the substrate is transformed to an enzymatic reaction product by the COX-2 enzyme, and is also significantly transformed to a reaction product by the COX-1 enzyme, then the substrate is not a COX-2 selective substrate of the present invention. Furthermore, this is sufficiently described in the Specification. For example, see pages 10-11. One of ordinary skill in the art can certainly make that determination, and the Office Action does not provide supported reasoning to the contrary.

Further, the Specification provides multiple examples of a "COX-2 selective substrate" of the present invention. For example, see page 17, lines 25-27 – page 18, line 3. These examples include 2-AG, and AEA. In the context of claim 23 and the aforementioned examples, a metabolite of 2-AG or AEA may be detected in accordance with the claimed method. As stated on page 18, lines 2-3, "COX-1 does not form significant amounts of PG-G products." On the other hand, arachidonic acid is not a COX-2 selective substrate since, as indicated by FIG 2, it is significantly transformed by the COX-1 enzyme as well.

At best, the language of claims 23 and 33 render them broad, but not indefinite. However, the breadth of a claim is not the correct standard for determining obviousness. See *In re Miller*, 169 U.S.P.Q. 597 (CCPA 1971) ("Breadth of a claim is not to be equated with indefiniteness.").

Claim 25

Claim 25 is allegedly unclear because it "does not tell what is being related between the detection of the metabolite to the status of COX-2 enzymatic activity." This position is respectfully traversed, but is moot in view of the above claim amendment. Claim 25 was amended to include a feature of "relating said amount of the COX-2 specific metabolite to the activity of the COX-2 enzyme."

In view of the above, Applicants' respectfully request that this rejection be withdrawn.

Issues Under 35 U.S.C. § 112, First Paragraph

The rejection of claim 9 under 35 U.S.C. § 112, first paragraph is moot in view of the cancellation of claim 9.

Claims 1-3, 5-16, 18-26, and 28-38 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled. The Office Action alleges that metabolites other than HETE-G, PGE_2-G, and 6-keto-$PGF_{1\alpha}$-G are not enabled by the specification.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Teletronics, Inc.*, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985).

It is clear that the burden is on the Examiner to establish a reasonable basis to question the enablement provided in the claimed invention. M.P.E.P. § 2164.04. Applicants respectfully submit that the Office Action fails to present a reasonable basis to question enablement. There is considerable direction and guidance in the Specification, and all of the methods needed to practice the invention are well known.

Specifically, (i) an example of a detection device is provided on page 25, (ii) multiple examples are provided demonstrates how to collect, detect and measure metabolites of the present invention (See at least Examples 1-8), (iii) at least one section of the Specification is dedicated to measuring metabolites of the present invention (See Section 4.4 MEASURING GLYCERYL-PROSTAGLANDINS), and (iv) many metabolites are listed in the Specification (see page 11, for example). Furthermore, (v) figures are provided that show metabolic pathways to arrive at metabolites of the present invention.

The Office Action states that (1) "The specification teaches... that not all COX-2 specific metabolites are detected" (citing Fig. 11, Fig. 12, and page 34 of the Specification) and (2) the LaPointe et al. reference teaches "that not all COX-2 metabolites are stable enough to be detected.

Applicants respectfully submit that the interpretation of the Specification is incorrect. For example, Fig. 11 identifies exemplary gylceryl esters of the present invention, rather than indicate that "not all COX-2 specific metabolites are detected." Page 27 of the Specification lists examples of samples (e.g., blood, saliva, tumor cells, etc.). Different metabolites may be present in different amounts depending on the sample (see below).

Page 34, line 23 of the Specification states that "[a]lthough the PGI_2-G was not directly detected in the experiments performed, it is a necessary intermediate for the production of 6-keto-$PGF_{1\alpha}$-G by the action of COX-2 and PGIS." The Office Action improperly associates this statement with the argument that "not all COX-2 specific metabolites are detected." As is clear from the above statement (as well as, for example, page 18, lines 18-19, and Fig. 6), it is clear that in the case of PGI_2-G, downstream metabolites (such as 6-keto-$PGF_{1\alpha}$-G, a preferred embodiment) are preferably detected and are indicative of COX-2 activity.

Finally, the Office Action cites the LaPointe et al. reference as indicating "that not all COX-2 metabolites are stable enough to be detected." The statement from the reference cited by the Examiner indicate that 6-keto-$PGF_{1\alpha}$ is "the stable metabolite of PGI_2." Again, for the reasons stated above, it does not follow from such a statement that one of ordinary skill in the art cannot detect a metabolite of the present invention. The Specification gives an example of a downstream metabolite that may be preferably detected in the place of PGI_2. Furthermore, the LaPointe et al. reference does not disclose the COX-2 specific metabolites of the present invention (see below). There is support that prostaglandin glycerol esters are sufficiently stable in plasma, whole blood, and cerebrospinal fluid. See Kozak et al. (2001) J. Biol. Chem. 276:36993-36998, attached to this Amendment.

In summary, the arguments with respect to a lack of enablement is unsupported and conclusory. The Examiner has provided no evidence, supported by a journal article or the like, indicating that one of ordinary skill in the art cannot identify the metabolites of the present invention.

In view of the above, Applicant's respectfully request that this rejection be withdrawn.

Issues Under 35 U.S.C. § 102

Claims 23-25, and 33 are rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Futaki et al., LaPointe et al., Hamilton et al., Belvisi et al., or Lundy et al. (cited in the Office Action as WO 98/50033). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The cited references disclose methods of detecting COX-2 enzymatic activity by detecting 6-keto-$PGF_{1\alpha}$. 6-keto-$PGF_{1\alpha}$ is a metabolite of PGH_2, which is the product of COX oxygenation of arachidonic acid.

However, the cited references fail to disclose or suggest the step of detecting a COX-2 specific metabolite, or detecting a metabolite of a COX-2 selective substrate.

In order to anticipate a claim, each and every element as set forth in the claim must be described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, the identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). Applicants respectfully submit that in view of the deficiencies discussed above, it is clear that the references cited above do not anticipate the present invention.

As stated above, the cited references disclose methods of detecting COX-2 enzymatic activity by detecting 6-keto-$PGF_{1\alpha}$. 6-keto-$PGF_{1\alpha}$ is a metabolite of PGH_2, which is the product of COX oxygenation of arachidonic acid (AA). AA is oxidized at equivalent rates by COX-1 and COX-2. Therefore, there can be no inherent preference for the production of 6-keto-$PGF_{1\alpha}$ by COX-2.

COX-2 selective inhibitors reduce production of urinary 6-keto-$PGF_{1\alpha}$ and its metabolites by 65% in humans. Thus, the maximal "selectivity" observable by monitoring 6-keto-$PGF_{1\alpha}$ is 65% / 35%, or 1.85.This contrasts dramatically with the inherent selectivity of COX-2 oxidation of arachidonyl esters, for example, which ranges from at least 10-100 fold.

Without being bound by theory, the cellular source of increased 6-keto-$PGF_{1\alpha}$ is believed to be vascular endothelial cells. These cells contain high concentrations of PGI synthase, which converts PGH_2 to PGI_2, the precursor to 6-keto-$PGF_{1\alpha}$. Many other cell types that can be induced to express COX-2 (e.g., macrophages, neurons, tumor) do not express significant amounts of PGI synthase. So, even though COX-2 is highly induced in other tissues, the level of 6-keto-$PGF_{1\alpha}$ will not increase.

The present invention is based on the selective oxygenation of AA derivatives by COX-2. This includes the prostaglandin glycerol esters (PG-Gs), examples with respect to the present invention. For example, any metabolite of PGH_2-G, formed in any tissue will reflect the selective action of COX-2.

As a result, the present invention provides significant advantages over the prior art, such as the ability to detect and/or quantify COX-2 directly in a patient or sample thereof.

In view of the above, Applicants respectfully request that this rejection be withdrawn.

Issues under 35 U.S.C. § 103

Claims 1-39 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Kalgutkar et al., in view of Felder et al., and further in view of a third reference, Lundy et al.

(WO 98/50033). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are respectfully requested.

Kalgutkar et al. disclose procedures to increase the COX-2 selectivity of indomethacin compounds. As stated by the Examiner, the reference fails to disclose or suggest 2-AG (and its role in COX-2 activity or detection).

Lundy et al. fail to disclose or suggest the step of detecting a COX-2 specific metabolite, or detecting a metabolite of a COX-2 selective substrate.

Felder et al. discusses cannabinoid receptor physiology the receptor's roles in binding the active principle in marijuana and anandamide. Felder et al. fail to disclose or suggest, among other things, detection of COX enzymes.

To establish a *prima facie* case of obviousness, there must be some motivation to combine the references with a reasonable expectation of success. See M.P.E.P. § 2142. Additionally, the references, when combined, must teach or suggest all of the claim limitations. The teaching or suggestion must be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that the references cannot be combined in the manner suggested by the Examiner. More specifically, the Office Action provides no support or explanation as to what would lead one of ordinary skill in the art would pick and choose a 2-AG compound from a non-COX-related reference, and substitute it for a structurally unrelated indomethacin compound, and then detect a metabolite of the 2-AG compound to determine an activity of a COX-2 enzyme – a step that is not disclosed in any of the references. The Federal Circuit stated that conclusions of obviousness must be specifically supported or explained. *See In*

re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Applicants respectfully submit that the Office Action is silent as to the interchangeability of the cited references.

At best, the Office Action outlines an "obvious to try" situation where the instant disclosure is used as a blueprint to find prior art corollaries for the claimed elements, and piecing together the elements of the prior art in an attempt to negate patentability. This method has repeatedly been frowned upon by the courts. For example, see *Sensonics, Inc. v. Aerosonic Corp.*, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996) ("an illogical and inappropriate process by which to determine patentability").

Even of the references were combined, they fail to disclose or suggest all the claims limitations. As stated by the Examiner, neither the primary or secondary reference discloses 2-AG. Furthermore, Applicants respectfully submit that none of the cited references disclose or suggest detecting a COX-2 specific metabolite of 2-AG. Further, none of the cited references disclose or suggests (1) adding a COX-2 selective substrate to a subject and (2) detecting a metabolite of the COX-2 selective substrate. Such deficiencies certainly are not remedied by the Felder et al. reference, which is nonanalogous to COX activity.

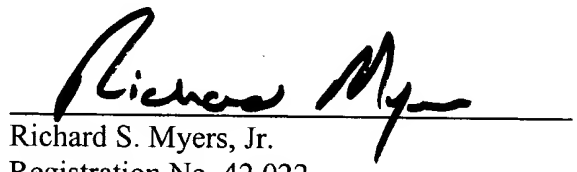
Thus, because there would be no motivation to combine the cited references to arrive at the present invention, and because the cited references fail to disclose each feature of the rejected claims, the present invention is clearly not obvious in view of the above-cited references.

In view of the above, Applicants respectfully request that this rejection be withdrawn.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants hereby petition for a one-month extension of time for filing a response to the outstanding Office Action. A check in the amount of $55.00 for the extension of time fee is attached.

If the Examiner has any questions concerning this election or the Application in general, he is respectfully requested to contact the undersigned at the number listed below.

Respectfully submitted,



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Version with Markings to Show Specification and Claim Amendments Made

In the Specification

The paragraph beginning at page 12, line 26 of the Specification:

"The state of a tumor refers to the extent of a cancer, how advanced the tumor is in the patient (*e.g.*, whether the disease has spread from the original site to other parts of the body). The stage of a tumor is generally determined by radiographic studies such as a computed tomography (CT) scan. magnetic resonance (MRI) imaging and/or ultrasound. Tumor staging is determined by one of ordinary skill in the art and can vary by tumor type or as a field advances, standard staging practices may change. Certain definitions of stages for various cancers are provided in the Dictionary of Cancer Terms [on CANCERNET] which is a service of the National Cancer Institute [available on the World Wide Web at "http://cancernet.nci.nih.gov/dictionaryfull.html", incorporated herein by reference in its entirety]. A physical location for inquiry or obtaining a copy of the Dictionary of Cancer Terms is: NCI Public Inquiries; Building 31; Room 10A03; 31 Center Drive, MSC 2580; Bethesda, MD 20892-2580.

In the Claims

Claim 1 (Amended). A method of detecting an activity of a COX-2 enzyme in a subject, comprising:

a) obtaining a sample of the subject; and

b) detecting a COX-2 specific metabolite of a 2-arachidonylglycerol compound in the sample, wherein the presence of the COX-2 specific metabolite in the sample indicates the activity of the COX-2 enzyme in the subject.

Claim 13 (Amended). A method of measuring an activity of a COX-2 enzyme in a subject, comprising:

a) obtaining a sample of the subject;

b) measuring an amount of a COX-2 specific metabolite of a 2-arachidonylglycerol compound in the sample; and

c) relating the amount of the COX-2 specific metabolite to the activity of the COX-2 enzyme.

Claim 14. The method of Claim 13, further comprising comparing the amount measured to a standard value, which correlates to an amount of signal with a known amount of a COX-2 specific metabolite of a 2-arachidonylglycerol compound.

Claim 25. The method of claim 24, further comprising relating the amount of the metabolite in the sample to the activity of the COX-2 enzyme in the subject, and relating said amount of the COX-2 specific metabolite to the activity of the COX-2 enzyme.